Use of Montelukast in Seasonal Allergic Rhinitis

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

INTRODUCTION

Leukotrienes trigger a number of effects that have been connected with symptoms of both asthma and allergic rhinitis. Leukotrienes have been associated with both the early and late stages of allergy symptoms; symptoms commonly experienced during the early stages of allergies include sneezing, nasal itching and runny nose; late stage symptoms include congestion.

Montelukast was approved on January 2, 2003 for relief of symptoms of seasonal allergic rhinitis for adults and children $\geq$ 2 years of age. Montelukast has not been evaluated for perennial allergic rhinitis. The class review of leukotrienes inhibitors had been previously presented.

EFFICACY

The following table lists the different efficacy endpoints used in the clinical trials and a short description of how the scores are calculated.

Table 1. Scales and measures used to evaluate efficacy

Total daytime nasal sx scores	Mean of 4 individual scores (congestion, rhinorrhea, nasal pruritus, sneezing). Each sx scored 0-3 with 0=none, 1= mild (sx noticeable but not bothersome), 2=moderate (sx noticeable and bothersome some of the time), 3= severe (sx bothersome most of the time/ very bothersome some of the time)
Nighttime symptom scores	Mean of 3 individual scores (difficulty falling asleep, nighttime awakenings, and nasal congestion on awakening). Each sx scored 0-3. For difficulty falling asleep 0= not at all, 1= little, 2= moderate, 3= very. For nighttime awakenings 0= not at all, 1= once, 2= more than once, 3= awake all night. For nasal congestion on awakening used same scoring as for nasal sx score.
Daytime eye symptoms score	Mean of 4 individual scores (tearing, itchy, red, puffy eyes). Each sx scored 0-4 with 0=none, 1= mild (sx noticeable but not bothersome), 2=moderate (sx noticeable and bothersome some of the time), 3= severe (sx bothersome most of the time/ very bothersome some of the time).
Daily composite symptoms score	Mean of the daytime nasal symptoms score and nighttime symptoms score
Interference with daily activity scores	11 point scale (0 no interference- 10 maximal interference)
Patient and physician global score	Compared to when entering the study, nose and nonose symptoms were rated on 7 point scale from 0 (very much better) – 3 (unchanged) - 6 (very much worse)
Rhinoconjunctivitis quality of life (RQLQ)	Made up of 28 items and 7 domains: activity, sleep, nasal symptoms, ocular symptoms, non-nose/non-eye symptoms, practical problems, and emotions. Each item is rated from 0 (not troubled) – 6 (extremely troubled)
Nasal peak inspiratory flow rate	Has been used to objectively measure nasal airflow obstruction and has shown good correlation with patients' rhinitis symptoms and treatment response (r= -0.51)

Montelukast vs. loratadine

There are 4 large randomized double-blind studies of 2 weeks duration. The primary outcome for all 4 studies was the improvement in daytime nasal symptom score.

In the study by Meltzer, improvement in the morning nasal score with montelukast 10mg or 20mg alone or loratadine 10mg alone was not significantly different from that seen with placebo. The combination of montelukast 10mg and loratadine 10mg resulted in significant improvement compared to placebo. Secondary outcomes such as morning eye symptom score, evening symptom score, and composite symptom score showed significant improvement in with montelukast 10mg and the combination of montelukast + loratadine compared to placebo. The improvement in the rhinoconjunctivitis quality of life score and the percentage of patients, who were better based on the patient global evaluation, were significant for all active treatment groups.[1]

In another study, morning nasal score improved with montelukast 10mg alone, loratadine 10mg alone, and the combination of the 2 when compared to placebo. Additionally, all active treatments showed significant improvement in all secondary outcomes, with the exception of the patient and physician global evaluations where only loratadine and the combination of loratadine + montelukast resulted in significant improvement. For all outcomes, when combination treatment was compared to each individual agent, the improvement was numerically greater with combination; however, statistical significance was not reached.[2]

Van Adelsberg et al. evaluated monotherapy with montelukast 10mg, loratadine 10mg, and placebo. The change from baseline with montelukast for all outcomes was significant compared to placebo except for the end-of-day nasal and end-of-day eye symptoms. Improvement with loratadine compared to placebo was significant for all outcomes except for nighttime symptoms. When montelukast and loratadine were compared, treatment favored loratadine for daytime eye symptoms and end-of-day nasal and end-of-day eye symptoms.[3]

In the study by Philip et al. monotherapy with montelukast 10mg or loratadine 10mg resulted in significant improvement compared to placebo for all measured outcomes. The 2 active treatments were not compared to each other.[4]

Montelukast, nasal steroids, non-sedating antihistamines

There are several smaller studies that looked at montelukast, nasal steroids, and antihistamines in a variety of combinations.

Pullerits et al. compared fluticasone nasal 200mcg daily, montelukast 10mg daily, and the combination of montelukast 10mg + loratadine 10mg daily. For daytime nasal symptom scores, only fluticasone and combination montelukast + loratadine showed significant improvement compared to placebo. Significant improvement with montelukast alone occurred during the last 2 weeks of the trial. For nighttime symptom scores, fluticasone was superior to all other treatment arms during weeks 3-5 and superior to montelukast during weeks 6-8. Combination montelukast + loratadine showed significant improvement by weeks 6-8. At no time point were the changes in the montelukast group significant to placebo.[5]

In 4 separate studies, Wilson et al. evaluated nasal peak inspiratory flow rate (PIFR) as the primary outcome. Secondary outcomes included, nasal symptom score, eye symptom score, daily activity score.

Cetirizine 10mg alone, cetirizine 10mg + mometasone 200mcg, and cetirizine 10mg + montelukast 10mg were evaluated. This study was not powered to compare differences between treatment arms; therefore, all comparisons were made versus baseline. Evening nasal inspiratory flow rate significantly improved for all treatment groups; however, daytime nasal PIFR showed significant improvement only for the cetirizine + mometasone combination. All secondary outcomes were improved in the cetirizine + mometasone group. Cetirizine alone led to significant improvement in all symptom scores except for the eye score. The combination cetirizine + montelukast group showed improvement in all symptoms scores except for the throat score and daily activity score.[6]

In a crossover study, patients received mometasone 200mcg and combination montelukast 10mg+ cetirizine 10mg. Compared to placebo, both treatments resulted in improvement in all outcomes. There were no significant differences between the two active treatments.[7]

In another study, patients with seasonal allergic rhinitis and stable asthma received both orally inhaled budesonide 400mcg + nasally inhaled budesonide 200mcg, and montelukast 10mg + cetirizine 10mg in a crossover fashion. Compared to the placebo period, all outcomes were improved with the steroids. With montelukast + cetirizine, all outcomes except nasal PIFR and eye symptom score significantly improved. Comparisons between active treatments were not made.[8]

Lastly, fexofenadine 120mg and montelukast 10mg + cetirizine 10mg were administered in a crossover fashion. Both treatments resulted in improvement in all outcomes compared to the placebo period. The difference between the 2 active treatments was not significant.[9]

Montelukast in the treatment of allergic rhinitis

<table>
<tr><th>Study</th><th>Entry criteria</th><th>Dosing</th><th>Measured outcomes</th><th>Baseline Information</th><th>Results</th></tr>
<tr>
<td>Meltzer 2000[1]
R, DB, PC, PR
Multicenter
Montelukast vs. loratadine vs. montelukast + loratadine vs. placebo
2 weeks
N=460
ITT</td>
<td>15-75 y/o
Spring SAR ≥ 2 yrs + skin test to ≥ 1 of 8 tree or grass pollens
Total daytime sx score ≥ 42 out of 84
Daytime congestion score ≥ 13 out of 21

Pts. with asthma using only SABAs were not excluded</td>
<td>1 week placebo run-in

Montelukast 10mg or
Montelukast 20mg or
Loratadine 10mg or
Montelukast 10mg + loratadine 10mg or
Placebo

Antihistamines, any steroids, cromolyn, nedocromil, inhaled anticholinergics, oral/LABAs, decongestants, were not allowed</td>
<td>1° outcomes
Total daytime nasal sx score 80% power to detect a between-tx difference of 0.25 score change from baseline
2° outcomes
Individual nasal scores, daytime eye sx scores, nighttime sx scores
Rhinoconjunctivitis QOL (RQOL)
Pt. global evaluation
Physician global evaluation
Composite score</td>
<td>% male – 36.7 – 49.5%
Duration of allergic rhinitis (years)- 17-18 yrs ± 13
% with conjunctivitis – 86.7 - 96.7
% h/o asthma – 20.9-35.9
Daytime nasal sx score- 2.02-2.12 ± 0.4
Daytime eye sx score- 1.31-1.47 ± 0.72
Nighttime sx score- 1.41 – 1.51 ± 0.61
Composite sx score – 1.77-1.86 ± 0.42
RQOL- 3.06-3.33 ± 1.0

Mean ± SD
Range of mean values</td>
<td>
<table>
<tr><th></th><th>MNT 10 N=95</th><th>MNT 20 N=90</th><th>LOR 10 N=92</th><th>MNT 10 +LOR 10 N=90</th><th>PL N=91</th></tr>
<tr><td>d/c all</td><td>5.3%</td><td>6.6%</td><td>5.4%</td><td>4.4%</td><td>6.6%</td></tr>
<tr><td>d/c 2° AE</td><td>0%</td><td>2.2%</td><td>2.2%</td><td>1.1%</td><td>3.3%</td></tr>
<tr><td>d/c 2° LOE</td><td>0%</td><td>2.2%</td><td>2.2%</td><td>0%</td><td>1.1%</td></tr>
<tr><td>AM nasal score</td><td>-0.36 [-0.47, 0.26]</td><td>-0.29 [-0.39, 0.18]</td><td>-0.34 [-0.44, 0.23]</td><td>-0.61* [-0.72, -0.51]</td><td>-0.25 [-0.36, -0.15]</td></tr>
<tr><td>AM eye sx score</td><td>-0.28* [-0.4, -0.15]</td><td>-0.14 [-0.27, 0.02]</td><td>-0.25 [-0.37, 0.12]</td><td>-0.46* [-0.59, -0.33]</td><td>-0.08 [-0.21, 0.05]</td></tr>
<tr><td>PM sx score</td><td>-0.29* [0.39, -0.19]</td><td>-0.21 [-0.31, 0.1]</td><td>-0.19 [-0.3, 0.09]</td><td>-0.33* [-0.43, -0.22]</td><td>-0.11 [-0.22, -0.01]</td></tr>
<tr><td>Composite Sx score</td><td>-0.39* [-0.48, -0.3]</td><td>-0.31 [-0.41, 0.22]</td><td>-0.32 [-0.41, 0.22]</td><td>-0.54* [-0.64, -0.44]</td><td>-0.24 [-0.34, -0.15]</td></tr>
<tr><td>RQOL</td><td colspan="5">M10 + L*, L*, M10* sig. improvement in scores</td></tr>
<tr><td>Pt global eval (% better/ no Δ/ worse)</td><td>54*/29/17</td><td>54*/27/19</td><td>58*/29/13</td><td>64*/25/11</td><td>40/34/26</td></tr>
</table>
Least square mean [95% CI]
*Significant vs. Placebo
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<tr>
<td>Nayak 2002[2]
R, DB, PC, PR
Multicenter
Montelukast vs. loratadine vs. montelukast + loratadine vs. placebo
2 weeks
n=907
ITT</td>
<td>15-85 y/o
Nonsmoking
Fall SAR ≥ 2 yrs. + skin test ≥ 1 allergen during fall
Daytime nasal score ≥ 42 over 7-day run-in

pts. with mild asthma using only SABAs were not excluded</td>
<td>1 week placebo run-in
1:2:2:1 randomization

Montelukast 10mg or
Loratadine 10mg or
Montelukast 10mg + loratadine 10mg or
Placebo

Antihistamines, any steroids, cromolyn, nedocromil, inhaled anticholinergics, oral/LABAs, theophylline,</td>
<td>1° outcomes
Total daytime nasal sx score 80% power to detect a 0.12 difference change from baseline between combination MNT/LOR and MNT
2° outcomes
Daytime eye sx scores, nighttime sx scores, daily composite sx score, individual nasal sx scores, individual</td>
<td>Age –35-38 ± 13
% male –31 –42%
Duration of allergic rhinitis (years)- 18 –20 ± 13
% with conjunctivitis – 89-93
% h/o asthma – 18-24
Daytime nasal sx score- 2.01-2.09 ± 0.4
Daytime eye sx score- 1.31-1.38 ± 0.75
Nighttime sx score- 1.32 – 1.50 ± 0.65
Composite sx score – 1.71-1.82 ± 0.45
RQOL- 3.06-3.25 ± 1.0</td>
<td>
<table>
<tr><th></th><th>MNT 10 N=155</th><th>LOR 10 N=301</th><th>MNT + LOR N=302</th><th>PL N=149</th></tr>
<tr><td>d/c all</td><td>4%</td><td>9%</td><td>5%</td><td>4%</td></tr>
<tr><td>d/c 2° AE</td><td>0</td><td>N=1</td><td>N=2</td><td>N=2</td></tr>
<tr><td>d/c 2° LOE</td><td>N=2</td><td>N=1</td><td>N=4</td><td>0</td></tr>
<tr><td>AM nasal score</td><td>-0.48 [-0.57, -0.40]*</td><td>-0.52 [-0.58, -0.46]*</td><td>-0.58 [-0.64, -0.51]*</td><td>-0.26 [-0.34, -0.17]</td></tr>
<tr><td>PM sx score (diff from PL)</td><td>-0.17 [-0.28, -0.07]*</td><td>-0.14 [-0.23, -0.05]*</td><td>-0.16 [-0.26, -0.07]*</td><td></td></tr>
<tr><td>Composite sx score (diff from PL)</td><td>-0.20 [-0.31, -0.10]*</td><td>-0.21 [-0.30, -0.12]*</td><td>-0.25 [-0.34, -0.16]*</td><td></td></tr>
<tr><td>AM eye sx</td><td>-0.20 [-0.32,</td><td>-0.23 [-0.34,</td><td>-0.27 [-0.37, -</td><td></td></tr>
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<tr>
<td></td>
<td></td>
<td>decongestants, anti-inflammatory drugs were not allowed</td>
<td>nighttime sx scores, Pt. and physician global evaluation, Rhinoconjunctivitis QOL (RQOL), blood eosinophil counts</td>
<td>Mean ± SD
Range of mean values</td>
<td>
<table>
<tr><td>score (diff from PL)</td><td>-0.08]*</td><td>-0.13]*</td><td>0.17]*</td><td></td></tr>
<tr><td>Pt. global eval (% w/ score of 0, 1, or 2)</td><td>62%</td><td>66%*</td><td>68%*</td><td>59%</td></tr>
<tr><td>MD global eval (% w/ score of 0, 1, or 2)</td><td>61%</td><td>63%*</td><td>64%*</td><td>56%</td></tr>
<tr><td>Eosinophils (cells/μL)</td><td>-30</td><td>No change</td><td>-20</td><td>No change</td></tr>
<tr><td>RQOL</td><td>-1.09 [-1.26, -0.92]*</td><td>-1.06 [-1.19, -0.93]*</td><td>-1.16 [-1.29, -1.03]*</td><td>-0.8 [-0.98, -0.63]</td></tr>
</table>
*Significant vs. placebo
Differences between combination tx vs. each individual agent not significant
LS mean [95% CI]
</td>
</tr>
<tr>
<td>Van Andelsberg[3]
2003
R, DB, DD, PC, PR
Multicenter
Montelukast vs. loratadine vs. placebo
2 weeks
N=1214
ITT</td>
<td>15-85y/o
Spring SAR ≥ 2 yrs
≥18 on 3-day cumulative daytime nasal score
+skin test to ≥ 1 allergen during study season
Non smoker

Pts. with asthma using only SABAs were not excluded</td>
<td>3-5 day placebo run-in

3:1:3 randomization
Montelukast 10mg or
Loratadine 10mg or
Placebo

Antihistamines, any steroids, any cromolyn or nedocromil, inhaled anticholinergics, oral/LABA, theophylline were not allowed</td>
<td>1° outcomes
Total daytime nasal sx score 93% power to detect a difference between montelukast and placebo of 0.15 score change from baseline
2° outcomes
Individual nasal scores, daytime eye sx scores, nighttime sx scores
Rhinoconjunctivitis QOL (RQOL)
Pt. global evaluation
Physician global evaluation
Blood eosinophil</td>
<td>% male –34-42%
Duration of allergic rhinitis (years)- 17-18 yrs ± 12
% with conjunctivitis –88-89%
% h/o asthma – 23-26%
Daytime nasal sx score- MNT 2.1 ± 0.43; LOR 2.15 ± 0.45; PL 2.14 ± 0.43
Daytime eye sx score- MNT 1.49 ± 0.77; LOR 1.48 ± 0.79; PL 1.53 ± 0.81
Nighttime sx score- MNT 1.51 ± 0.65; LOR 1.49 ± 0.64; PL 1.47 ± 0.65
Composite sx score – MNT 1.85 ± 0.45; LOR 1.86 ± 0.43; PL 1.85 ± 0.45
RQOL- MNT 3.22 ± 1.06; LOR 3.24 ± 0.97; PL 3.29 ± 1.01

Mean ± SD</td>
<td>
<table>
<tr><th></th><th>MNT n=522</th><th>LOR n=171</th><th>PL n=521</th></tr>
<tr><td>d/c all</td><td>4%</td><td>3.5%</td><td>5.6%</td></tr>
<tr><td>d/c 2° AE</td><td>1.3%</td><td>0.6%</td><td>1.5%</td></tr>
<tr><td>d/c 2° LOE</td><td>1.0%</td><td>1.1%</td><td>2.7%</td></tr>
<tr><td>AM nasal score</td><td>-0.38*
[-0.45, -0.33]</td><td>-0.47*
[-0.55, -0.39]</td><td>-0.29
[-0.33, -0.24]</td></tr>
<tr><td>AM eye sx score</td><td>-0.28*
[-0.32, -0.23]</td><td>-0.40*^
[-0.47, -0.32]</td><td>-0.21
[-0.25, -0.16]</td></tr>
<tr><td>PM sx score</td><td>-0.28*
[-0.32, -0.24]</td><td>-0.28
[-0.35, -0.21]</td><td>-0.20
[-0.25, -0.16]</td></tr>
<tr><td>Composite Sx score</td><td>-0.34*
[-0.38, -0.30]</td><td>-0.39*
[-0.46, -0.32]</td><td>-0.25
[-0.29, -0.21]</td></tr>
<tr><td>RQOL</td><td>-0.90*
[-1.00, -0.81]</td><td>-0.98*
[-1.15, -0.81]</td><td>-0.66
[-0.76, -0.56]</td></tr>
<tr><td>Pt global eval</td><td>2.18*
[2.05, 2.31]</td><td>2.19*
[1.97, 2.42]</td><td>2.49
[2.36, 2.62]</td></tr>
<tr><td>MD global eval</td><td>2.18*
[2.07, 2.3]</td><td>2.16*
[1.96, 2.35]</td><td>2.41
[2.29, 2.52]</td></tr>
<tr><td>End-of –day nasal sx</td><td>-0.30
[-0.35, -0.25]</td><td>-0.40*^
[-0.9, -0.32]</td><td>-0.24
[-0.28, -0.19]</td></tr>
<tr><td>End-of-day eye sx</td><td>-0.23
[-0.27, -0.19]</td><td>-0.35*^
[-0.43, -0.28]</td><td>-0.20
[-0.24, -0.15]</td></tr>
</table>
LS mean difference [95% CI]
*Significant vs. placebo
^Treatment favored LOR over MNT (CI for treatment differences not provided)
</td>
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</table>

<table>
<tr>
<td>Philip 2002[4]
R, DB, PR
Multicenter
Montelukast vs. loratadine vs. placebo
2 weeks
n=1302
ITT</td>
<td>15-81 y/o
Nonsmoking
SAR ≥ 2 yrs. w/ exacerbations during spring
+ skin test ≥ 1 allergen during spring
Nasal sx score ≥ 18

pts. with mild asthma using only SABAs were not excluded</td>
<td>3-5 day placebo run-in

Montelukast 10mg
Loratadine 10mg
Placebo

Antihistamines, any steroids, cromolyn, nedocromil, anticholinergics, oral/LABAs, theophylline, decongestants, were not allowed</td>
<td><u>1° outcomes</u>
Total daytime nasal sx score

<u>2° outcomes</u>
Daytime eye sx scores, nighttime sx scores, Pt. and physician global evaluation, Rhinoconjunctivitis QOL (RQOL), daily composite sx score, eosinophil counts</td>
<td>Age –36-37 ± 13
% male –65-67%
Duration of allergic rhinitis (years)- 18 ± 12
% with conjunctivitis – 87-90
% h/o asthma – 25-29
Daytime nasal sx score- 2.06-2.10 ± 0.43
Daytime eye sx score- 1.39-1.44 ± 0.76
Nighttime sx score- 1.43 – 1.46 ± 0.65
Composite sx score – 1.79-1.83 ± 0.45
RQOL- 3.09-3.22 ± 1.01

Range of mean values ± SD</td>
<td>
<table>
<tr><th></th><th>MNT N=348</th><th>LOR N=602</th><th>PL N=352</th></tr>
<tr><td>d/c all</td><td>3.4%</td><td>4.8%</td><td>5.1%</td></tr>
<tr><td>d/c 2° AE</td><td>0.9%</td><td>1.5%</td><td>0.3%</td></tr>
<tr><td>d/c 2° LOE</td><td>1.1%</td><td>1.3%</td><td>2.3%</td></tr>
<tr><td>AM nasal score (difference from PL)</td><td>-0.13 [-0.21, -0.06]*</td><td>-0.24 [-0.31, -0.17]*</td><td></td></tr>
<tr><td>AM nasal score (% change)</td><td>-18%*</td><td>-22%*</td><td>-9%</td></tr>
<tr><td>PM sx score (difference from PL)</td><td>-0.14 [-0.20, -0.07]*</td><td>-0.09 [-0.15, -0.03]*</td><td></td></tr>
<tr><td>PM sx score (% change)</td><td>-20%*</td><td>-15%*</td><td>-8%</td></tr>
<tr><td>Composite score (Difference from PL)</td><td>-0.13 [-0.20, -0.07]*</td><td>-0.17 [-0.24, -0.11]*</td><td></td></tr>
<tr><td>Composite score (% change)</td><td>-16%*</td><td>-20%*</td><td>-9%</td></tr>
<tr><td>AM eye sx score (difference from PL)</td><td>-0.14 [-0.22, -0.06]*</td><td>-0.20 [-0.28, -0.13]*</td><td></td></tr>
<tr><td>Eosinophils (% change)</td><td>-16.9%</td><td>0</td><td>+1.1%</td></tr>
<tr><td>RQOL</td><td>-0.89 [-1.01, -0.77]*</td><td>-0.99 [-1.08, -0.90]*</td><td>-0.65 [-0.76, -0.53]</td></tr>
</table>
*Significant vs. placebo
LS mean [95% CI]
</td>
</tr>
<tr>
<td>Pullerits 2002[5]
R, DB, PC, PR, DD
Fluticasone nasal vs. montelukast vs. montelukast + loratadine vs. placebo
50 days
N=62
ITT</td>
<td>Grass pollen induced AR during season for ≥ 2 years
15-50 y/o
+ skin test to grass pollen

pts. with perennial rhinitis were excluded</td>
<td>Fluticasone AQ nasal soln 200mcg
Montelukast 10mg
Montelukast 10mg + loratadine 10mg
Placebo

Cromoglycate eye drops and limited loratadine for rescue were allowed</td>
<td><u>1° outcomes</u>
Daytime nasal sx score
Nighttime nasal sx score

<u>2° outcomes</u>
Nasal EG2+ eosinophils (epithelial and subepithelial)</td>
<td>Mean age – 30yrs
Dur of AR > 5 yrs – 80%
Total daytime nasal sx score-
FP 1.5 ± 1.4; MNT 1.9 ± 2.1; MNT+LOR 1.9 ± 1.5; PL 2.4 ± 2.3
Total nighttime nasal sx score- FP 0.9 ± 1.2; MNT

Mean ± SD</td>
<td>
<table>
<tr><th></th><th>FP (n=13)</th><th>MNT (n=16)</th><th>MNT+LOR (n= 15)</th><th>PL (n=18)</th></tr>
<tr><td>Daytime nasal score (Weeks 1-2/ 3-5/6-8)</td><td>1.4 ± 0.7*
2.6 ± 1*
1.1 ± 0.5*^</td><td>2.6 ± 0.5
4.4 ± 0.6
2.2 ± 0.4*</td><td>2.1 ± 0.5*
4 ± 0.7*
1.5 ± 0.4*</td><td>3.5 ± 0.4
5.9 ± 0.6
3.3 ± 0.3</td></tr>
<tr><td>Nighttime nasal score (weeks 1-2/ 3-5/6-8)</td><td>0.7 ± 0.6*
1 ± 0.8 *^♦
0.4 ± 0.5*^</td><td>1.8 ± 0.4
2.8 ± 0.5
1.5 ± 0.3</td><td>1.3 ± 0.4
2.7 ± 0.6
1.2 ± 0.3*</td><td>2.1 ± 0.4
3.6 ± 0.5
2.3 ± 0.3</td></tr>
<tr><td>Epithelial EG2+ eos (cells/mm2)</td><td>0*^♦</td><td>+22.5</td><td>+36.2</td><td>+24.4</td></tr>
<tr><td>Subepithelial EG2+ eos (cells/mm2)</td><td>1.2</td><td>45.7</td><td>46.8</td><td>76</td></tr>
</table>
*Significant vs. placebo
^Significant vs. montelukast
♦Significant vs. montelukast + loratadine
Mean ± SEM
</td>
</tr>
</table>

<table>
<tr>
<td>Wilson 2000[6]
R, SB, PC, PR, DD
Cetirizine vs. cetirizine + mometasone vs. cetirizine + montelukast
4 weeks
N=38</td>
<td>16-65y/o
Symptomatic SAR with rhinorrhea, stuffiness, sneezing + skin test ≥ 1 pollen extract (grass, weed, tree)</td>
<td>1 week placebo run-in

Cetirizine 10mg vs. Cetirizine 10mg + mometasone nasal 200mcg vs. Cetirizine 10mg + Montelukast 10mg</td>
<td><u>1° outcomes</u>
Nasal PIFR 90% power to detect a 15L/min change
Nasal sx score

<u>2° outcomes</u>
Total daily symptom scores (sum of nasal, eyes, throat scores)
Interference with daily activity</td>
<td>Age – 31 ± 2.5 yrs.
% male – 68%
Nasal PIFR am (L/min) – CT 117 ± 12; CT + MM 103 ± 8; CT + MNT 102.5 ± 5
Nasal PIFR pm (L/min) – CT 115 ± 12; CT + MM 107 ± 9; CT + MNT 117 ± 7
Total daily sx score – CT 11.3 ± 2.0; CT + MM 10 ± 1.8; CT + MNT 10.4± 2.0
Total nasal – CT 5.3 ± 0.8; CT+MM 4.8 ± 0.7; CT+MNT 5.2 ± 0.8
Total eye – CT 2.4 ± 0.5; CT+MM 1.6 ± 0.4; CT+MNT 2.1 ± 0.6
Total throat – CT 1.1 ± 0.3; CT+MM 1.1 ± 0.2; C+MNT 0.7 ± 0.2
Daily activity – CT 3.5 ± 0.7; C+MM 2.6 ± 0.6; C+MNT 2.4 ± 0.6

Mean ± SEM</td>
<td>
<table>
<tr><th></th><th>CTZ</th><th>CTZ + MM</th><th>CTZ + MNT</th></tr>
<tr><td>Nasal PIFR am (L/min)</td><td>137 ± 16</td><td>136 ± 13*</td><td>123 ± 12</td></tr>
<tr><td>Nasal PIFR pm (L/min)</td><td>146 ± 14*</td><td>144 ± 17*</td><td>144 ± 13*</td></tr>
<tr><td>Total sx score</td><td>4.3 ± 1.4*</td><td>2.1 ± 1.1 *</td><td>5.5 ± 1.2*</td></tr>
<tr><td>Total nasal score</td><td>2.5 ± 0.8*</td><td>1.1 ± 0.6*</td><td>2.6 ± 0.5*</td></tr>
<tr><td>Total eye score</td><td>1.0 ± 0.4</td><td>0.4 ± 0.2*</td><td>0.9 ± 0.3*</td></tr>
<tr><td>Total throat score</td><td>0.1 ± 0.1*</td><td>0.4 ± 0.3*</td><td>0.2 ± 0.1</td></tr>
<tr><td>Daily activity</td><td>1.1 ± 0.4*</td><td>0.5 ± 0.3*</td><td>1.8 ± 0.5</td></tr>
</table>
*Significant vs. baseline
Mean ± SEM
Study not powered to compare differences between tx arms
</td>
</tr>
<tr>
<td>Wilson 2001[7]
R, SB, PC, CO, DD
Mometasone vs. montelukast + cetirizine
2 weeks each arm
n=22</td>
<td>Symptomatic SAR
No h/o asthma
+ skin prick test to grass, tree, or weed pollen
Nonsmokers</td>
<td>1 week placebo run-in and washout between treatments

Mometasone 200mcg vs. montelukast 10mg + cetirizine 10mg</td>
<td><u>1° outcomes</u>
Nasal PIFR powered to detect a 20% change

<u>2° outcomes</u>
Total nasal sx score
Eye sx score
Individual nasal sx score for blockage and itchiness
Interference with daily activity score</td>
<td>Age – 35 ± 13.1
Nasal PIFR (L/min)- 110 ± 4
Total nasal sx score- 3.5 ± 0.2
Daily activity score- 2.0 ± 0.2
Eye sx score- 1.9 ± 0.2

Mean ± SEM</td>
<td>
<table>
<tr><th></th><th>Mometasone</th><th>MNT + CTZ</th></tr>
<tr><td>Nasal PIFR (L/min)</td><td>133 ± 4*</td><td>124 ± 4*</td></tr>
<tr><td>Nasal sx score</td><td>1.55 ± 3*</td><td>1.6 ± 3*</td></tr>
<tr><td>Eye sx score</td><td>0.9 ± 0.2*</td><td>0.7 ± 0.2*</td></tr>
<tr><td>Daily activity score</td><td>0.8 ± 0.2*</td><td>0.9 ± 0.2*</td></tr>
</table>
Values for PIFR, nasal sx score, and daily activity score estimated from graph
Mean ± SEM
*Significant vs. placebo period
</td>
</tr>
</table>

<table>
<tr>
<td>Wilson 2001[8]
R, SB, PC, CO
Orally inhaled + nasally inhaled budesonide vs. montelukast + cetirizine
2 weeks each arm
n=21</td>
<td>SAR
Asthma
+ skin prick test grass, tree, weed or house dust mite
Nonsmokers</td>
<td>1 week placebo run-in and washout between treatments
Orally inhaled budesonide 400mcg + intranasal budesonide 200mcg vs.
Montelukast 10mg + cetirizine 10mg</td>
<td><u>1° outcomes</u>
Nasal PIFR powered to detect a 20% change

<u>2° outcomes</u>
Total nasal sx score
Individual nasal sx score for blockage and itchiness components
Eye sx score
Interference with daily activity score</td>
<td>Age- 32 ± 2.3yrs.
FEV1 % predicted- 83.5 ± 3.3
Nasal PIFR (L/min)- 116 ± 3
Total nasal sx score- 3.35 ± 0.31
Eye sx score- 1.92 ± 0.21
Throat sx – 0.49 ± 0.11
Daily activity score – 1.92 ± 0.24

Mean ± SEM</td>
<td>
<table>
<tr><th></th><th>BUD oral + intranasal</th><th>MNT + CTZ</th></tr>
<tr><td>Nasal PIFR (L/min)</td><td>127 ± 3*</td><td>121 ± 3</td></tr>
<tr><td>Nasal sx score</td><td>-1.4 [-0.3, -2.5]*</td><td>-2.0 [-0.9, -3.1]*</td></tr>
<tr><td>Eye sx score</td><td>0.94 ± 0.2*</td><td>1.14 ± 0.2</td></tr>
<tr><td>Throat sx</td><td>0.3 ± 0.1*</td><td>0.37 ± 0.1*</td></tr>
<tr><td>Daily activity score</td><td>0.63 ± 0.23*</td><td>0.82 ± 0.24*</td></tr>
</table>
*Significant vs. placebo period
Mean ± SEM
</td>
</tr>
<tr>
<td>Wilson 2002[9]
R, SB, PC, DD, CO
Fexofenadine vs. montelukast + loratadine
2 weeks each arm
N=37</td>
<td>SAR requiring tx
+ skin prick test to grass pollens
Nonsmokers
No h/o persistent asthma, use of ICS, FEV1 < 90% pred</td>
<td>7-10 day week placebo run-in and washout between treatments
Fexofenadine 120mg vs. montelukast 10mg + loratadine 10mg

Pts. allowed to use PRN ocular cromoglycate</td>
<td><u>1° outcomes</u>
Nasal PIFR powered to detect a 10L/min change

<u>2° outcomes</u>
Nasal sx score
Eye sx score
Daily activity score (4 point scale)</td>
<td>Age – 37 ± 2.0 yrs.
Nasal PIFR (L/min)- 102 [98, 97]
Total nasal sx score- 7.4 [6.7, 8.0]
Eye sx score – 4.0 [3.5, 4.6]
Daily activity score – 1.3 [1.1, 1.5]
Cromoglycate per day – 0.8 [0.6, 0.9]

Mean [95% CI]</td>
<td>
<table>
<tr><th></th><th>Fexofenadine</th><th>MNT + LOR</th></tr>
<tr><td>Completed study</td><td colspan="2">N=37</td></tr>
<tr><td>Nasal PIFR (L/min)</td><td>111 [107, 116]*</td><td>113 [109, 118]*</td></tr>
<tr><td>Nasal sx score</td><td>5.0 [4.3, 5.7]*</td><td>4.0 [3.3, 4.7]*</td></tr>
<tr><td>Eye sx score</td><td>2.5 [2.0, 3.1]*</td><td>1.8 [0.3, 2.4]*</td></tr>
<tr><td>Daily activity score</td><td>0.7 [0.5, 0.9]*</td><td>0.5 [0.3, 0.8]*</td></tr>
<tr><td>Cromoglycate use/d</td><td>0.3 [0.2, 0.5]*</td><td>0.3 [0.2, 0.5]*</td></tr>
</table>
*Significant vs. placebo period
No significant difference between active groups
Mean [95% CI]
</td>
</tr>
</table>

Abbreviations: AE=adverse event, CO=crossover, d/c=discontinued, DB=double-blind, DD=double-dummy, CTZ=cetirizine, FP=fluticasone propionate, ITT=intent to treat, LABA=long-acting beta-agonist, LOE=lack of efficacy, LOR=loratadine, MNT=montelukast, PIFR=peak inspiratory flow rate, PC=placebo-controlled, PL=placebo, PR=parallel, R=randomized, SABA=short-acting beta-agonist, SAR=seasonal allergic rhinitis, SB=single-blind

SAFETY

Hepatotoxicity

There have been no published reports of hepatotoxicity with montelukast since the last review.

Churg-Strauss Syndrome

Churg-Strauss syndrome (allergic angiitis and granulomatoses) is an uncommon syndrome that generally occurs in patients with asthma and allergic rhinitis. The hallmark features are eosinophilia ≥ 10% of WBC, mono- or polyneuropathy, pulmonary infiltrates, and eosinophilic vasculitis. Several cases of Churg-Strauss have been reported with leukotriene inhibitor use. In most cases, the leukotriene inhibitor was started while steroids were being withdrawn or within a few months of stopping steroids. This scenario has also occurred during systemic steroids withdrawal and initiation of inhaled steroids, theophylline, or cromolyn. One theory is that the syndrome is the result of unmasking a previously existing condition due to steroid withdrawal and not necessarily a direct effect of the leukotriene inhibitor. However, there have also been cases of antileukotriene-associated CSS in the absence of tapering oral steroids.

Using computerized claims data, Loughlin et al. attempted to calculate the background incidence rate of CSS in a cohort of asthma patients who have **not** used leukotriene receptor antagonists.[9] Definite CSS was defined as the patient having met criteria either as established by Lanham, American College of Rheumatology (ACR), or the Ingenix epidemiology adaptation of ACR. Patients were also evaluated for probable CSS, which was defined in the Ingenix epidemiology adaptation of ACR.

Using Lanham criteria, ACR, or Ingenix epidemiology adaptation of ACR, 0, 3, and 1 patient(s) respectively were identified as having definite CSS. The 44, 592 persons-years at risk generated incidence rates from 0 to 67 cases per 1,000,000 person-years depending on the definition of CSS used. Probable CSS was identified in 26 patients, which translates into an incidence rate of 583 per million person-years.

Twelve cases of CSS were identified from a MEDLINE search (7/2001 – 2/2003) using the terms montelukast and Churg-Strauss.[10-17]

Table 2. Reported cases of Churg-Strauss syndrome during montelukast therapy

Alonso, Sabio	2 cases with no prior oral or inhaled steroid use
Guilpan, Solans, Mateo, Perez de Llano, Turvey	4 cases with no prior history of oral steroid use, but the patients were taking ICS
Solans	1 case of a patient with a diagnosis of CSS well-controlled on 10mg/d of prednisone. One year later montelukast was started with subsequent exacerbation of CSS symptoms
Hammer	1 case of no prior oral steroid use with no mention in abstract if on ICS (article in Norwegian, abstract English)
Kalyoncu	Steroid dependent asthmatic with dose of prednisone reduced from 10mg daily to every other day. Montelukast begun 5 months later. CSS 2-3 months after montelukast was initiated.
Solans	ICS user with multiple courses of oral steroids last of which was 2 months prior to start of montelukast. CSS developed 10 days later
Guilpan	ICS user with 10-day course of oral steroid to treat asthma exacerbation. Montelukast also begun at that time. Four months later, patient diagnosed with CSS
Gal	Started on montelukast with 2-week taper of oral steroids. On month later, patient diagnosed with CSS

COST

Compared to antihistamines and nasally inhaled corticosteroids, montelukast is the most costly. Combination treatment with fexofenadine plus a nasal steroid (if using the national formulary product) is less than the price of montelukast alone.

Table. 3 Monthly cost of drugs used to treat AR*

Montelukast 10mg QD	$41.75
FEX 180mg FEX 30mg BID FEX 60mg BID	$18.00 $17.68 $22.20
Flunisolide (Bausch-Lomb) Flunisolide (Nasalide) Flunisolide (Nasarel)	$5.49 $6.18 $11.60
Fluticasone (Flonase)	$22.43
Mometasone (Nasonex)	$28.94
Triamcinolone (Nasacort) Triamcinolone AQ (Nasacort AQ)	$19.27 $21.87
Budesonide (Rhinocort) Budesonide AQ (Rhinocort AQ)	- $29.79

*Cost of inhalers based on 1 inhaler per month
For updated cost information, refer to www.vapbm.org

SUMMARY

Based on the available data, montelukast does not appear to have a clinical advantage over the other agents used to treat seasonal allergic rhinitis. In some of the smaller studies, combining montelukast + an antihistamine was as good as or slightly less effective than monotherapy with nasally inhaled steroids. In another small study, combining a nasal steroid + cetirizine had slightly better outcomes than the combination of montelukast + cetirizine. To date, there are no published studies evaluating combination treatment with montelukast + nasally inhaled steroids or the use of montelukast in managing perennial allergic rhinitis.

REFERENCES

1. Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol 2000; 105: 917-922.

2. Nayak AS, Philip G, Lu S, et al. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. Ann Allergy Asthma Immunol 2002; 88: 592-600.

3. van Adelsberg J, Philip G, LaForce CF, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2003; 90: 214-222.

4. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. Clin Exp Allergy 2002; 32: 1020-1028.

5. Pullerits T, Praks L, Ristioja V, et al. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2002; 109: 949-955.

6. Wilson A, Dempsey OJ, Sims EJ, et al. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy 2000; 30: 833-838.

7. Wilson AM, Orr LC, Sims EJ, et al. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. Clin Exp Allergy 2001; 31: 61-68.

8. Wilson AM, Sims EJ, Orr LC, et al. Effects of topical corticosteroid and combined mediator blockade on domiciliary and laboratory measurements of nasal function in seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2001; 87: 344-349.

9. Wilson AM, Orr LC, Coutie WJR, et al. A comparison of once daily fexofenadine versus the combination of montelukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis. Clin Exp Allergy 2002; 32: 126-132.

10. Loughlin JE, Cole JA, Rothman KJ, et al. Prevalence of serious eosinophilia and incidence of Churg-Strauss syndrome in a cohort of asthma patients. Ann Allergy Asthma Immunol. 2002 Mar; 88(3): 319-25.

11. Perez de Llano LA, Racamonde V, Parra Arrondo A. Sindrome de Churg-Strauss en un paciente asamatico tratado con montelukast: continuacion de una controversia. Arch Bronconeumol 2002; 38(5): 251-2.

12. Mateo ML, Cortes CM, Berisa F. Sindrome de Churg-Strauss asociado a la administraciond de montelukast en un paciente asmatico sin tratamiento esteroide de base. Arch Bronconeumol 2002; 38(1): 56.

13. Sabio JM, Jimenez-Alonso J, Gonzalez-Crespo F, et al. More about Churg-Strauss syndrome and montelukast treatment. Chest. 2001 Dec; 120(6): 2116.

14. Gal AA, Morris RJ, Pine JR, et al. Cutaneous lesions of Churg-Strauss syndrome associated with montelukast therapy. Br J Dermatol 2002; 147: 604-631.

15. Guilpain P, Viallard JF, Lagarde P, et al. Churg-Strauss syndrome in two patients receiving montelukast. Rheumatology 2002; 41: 535-539.

16. Solans R, Bosch JA, Selva A, et al. Montelukast and Churg-Strauss syndrome. Thorax 2002; 57: 183-185.

17. Kalyoncu AF, Karakaya G, Sahin AA, et al. Experience of 10 years with Chrug-Strauss syndrome: an accompaniment to or a transition from aspirin-induced asthma? Allergol et Immunopathol 2001; 29(5): 185-190.

18. Hammer HB, Aukrust P, Froland SS. Churg-Strauss syndrome after treatment with Singulair (montelukast). Tidsskr Nor Laegeforen 2002; 122 (5): 484-486.

19. Turvey SE, Vargas SO, Phipatanakul W. Churg-Strauss syndrome in a 7-year-old receiving montelukast and inhaled corticosteroids. Ann Allergy Asthma Immunol 2003; 90: 274.

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